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(54) Title: METHODS AND INTERMEDIATES FOR THE ASYMMETRIC SYNTHESIS OF CAMPTOTHECIN AND CAMPTOTHECIN ANALOGS		
<p>Chemical structures XIV, XV, XVII, and XVIII are shown. Structure XIV is a tricyclic compound with substituents OR₆, OR₇, R, and OR₈. Structure XV is similar to XIV but has a hydroxyl group at the position where OR₈ is located in XIV. Structure XVII is a bicyclic compound with substituents OR₆, OR₇, R, and OR₈. Structure XVIII is a cyclopentane ring with substituents Ru, R₁₁, R₁₂, and R₁₃.</p>		
(57) Abstract		
<p>Processes for making compounds of Formulae (XIV), (XV), and (XVII) wherein R₆ is lower alkyl, R₇ is lower alkyl, R is lower alkyl, Y is H, F or Cl, R₈ is a moiety of Formula (XVIII) wherein n is 1, 2 or 3, R₁₁ is C₁-C₄ alkyl and R₁₂ is the same as R₁₁, or R₁₁ and R₁₂ together form cyclopentane or cyclohexane, and R₁₃ is: (a) phenyl substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl, or (b) selected from the group consisting of naphthyl, anthryl, and phenanthryl optionally substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl groups, R₁₀ is C₆-C₁₀ alkyl, aryl or alkyl aryl, and Y is H, F or Cl, are disclosed. These processes can be used to make optically enhanced and optically pure forms of the compounds, which are useful in the making of a camptothecin and analogs thereof.</p>		

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METHODS AND INTERMEDIATES FOR THE ASYMMETRIC
SYNTHESIS OF CAMPTOTHECIN AND CAMPTOTHECIN ANALOGS

Field of the Invention

The present invention provides a parallel synthesis of camptothecin and camptothecin analogs via novel intermediates at high yields.

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Background of the Invention

Camptothecin (Chem. Abstracts Registry No. 7689-03-4) is a naturally occurring compound found in *Camptotheca acuminata* (Nyssaceae) which has antileukemic and antitumor properties. Numerous camptothecin analogs having like properties are known, examples being those described in U.S. Patent No. 4,894,456 to Wall et al. and European Patent Application No. 0 325 247 of Yaegashi et al.

A number of syntheses for camptothecin are known. Several routes are reviewed in Natural Products Chemistry, Vol. 2, 358-361 (K. Nakanishi, T. Goto, S. Itô, S. Natori and S. Nozoe eds.) and in J. Cai and C. Hutchinson, Camptothecin, in The Alkaloids,

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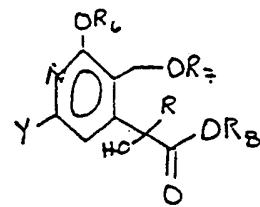
Vol. XXI, 101-137 (Academic Press 1983). The biosynthesis of camptothecin is described in Natural Products Chemistry, Vol. 3, 573-574 (K. Nakanishi et al. eds.). A recent synthetic route is described in 5 U.S. Patent No. 4,894,456 to Wall et al. (see also references cited therein).

A problem with prior methods of synthesizing camptothecin is that they are largely linear syntheses. Such syntheses provide low yields of the final product 10 because of the sequential loss in product during each step of the total synthesis. Parallel syntheses (i.e., a strategy in which two synthetic paths are followed separately and the products thereof combined to form the final product) provide higher yields, but few such 15 syntheses have been available for camptothecin. Accordingly, an object of the present invention is to provide a parallel synthetic method for making camptothecin and analogs thereof.

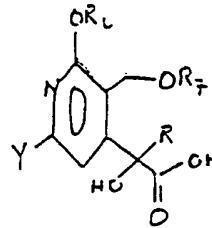
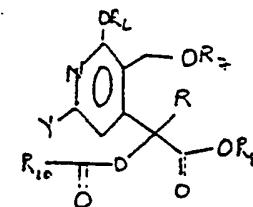
20 Summary of the Invention.

The present invention provides a process for making compounds of Formulae XIV, XV, and XVII below:

25



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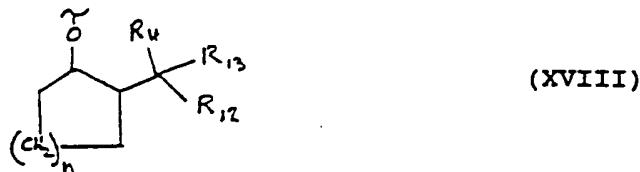
XIVXVXVI

wherein R₆ is lower alkyl, R₇ is lower alkyl, R is lower 35 alkyl, Y is H, F or Cl, R₈ is a compound of Formula XVIII

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15 wherein n is 1, 2, or 3, R₁₁ is C₁-C₄ alkyl and R₁₂ is the same as R₁₁, or R₁₁ and R₁₂ together form cyclopentane or cyclohexane, and R₁₃ is:

(a) phenyl substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl, or

20 (b) selected from the group consisting of naphthyl, anthryl, and phenanthryl optionally substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl groups,

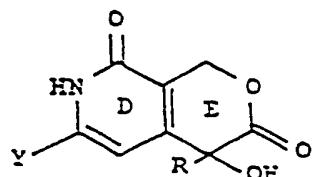
R₁₀ is C₆-C₁₀ alkyl, aryl or alkyl aryl,

25 and Y is H, F or Cl.

These compounds are useful in the production of compounds of Formula III,

30

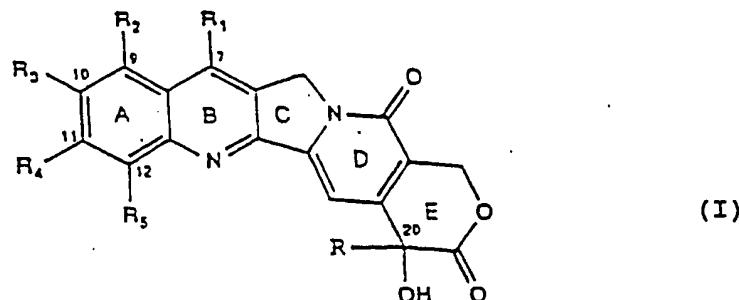
(III)



wherein R and Y are as defined above, which in turn is
35 useful in the production of compounds of Formula I.

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10 wherein:

R may be loweralkyl,

R₁ may be H, loweralkyl, loweralkoxy, or halo,R₂, R₃, R₄, and R₅ may each independently be H,

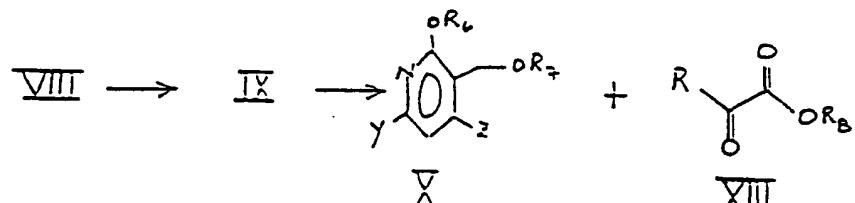
amino, hydroxy, loweralkyl, loweralkoxy,

15 loweralkylthio, di(loweralkyl)amino, cyano,
methylenedioxy, Formyl, nitro, halo, trifluoromethyl,
aminomethyl, azido, amido, hydrazino, or any of the
twenty standard amino acids bonded to the A ring via
the amino-nitrogen atom (numbering in Formula I is by
20 the Le Men-Taylor numbering system and rings are
lettered in the conventional manner. See J. Cai and C.
Hutchinson, supra at 102).

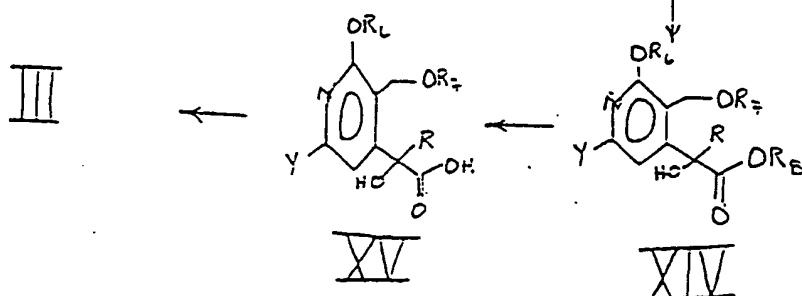
In one embodiment illustrated by Scheme D,

Scheme D

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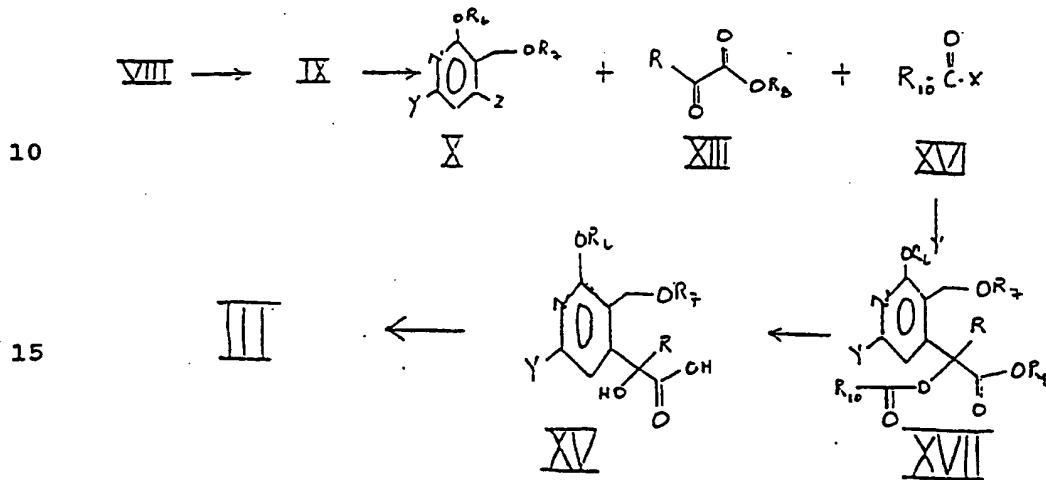
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R_8 is optically pure, which can lead to a diastereomerically enhanced compound XIV and optically enhanced compounds XV, III, and I. In another embodiment illustrated by Scheme E,

5

Scheme E

10 20 the use of optically pure R_8 can lead to a diastereomerically pure compound XVII, which in turn can be used to produce diastereometrically pure forms of compound XV and optically pure forms of compounds III and I.

25

Detailed Description of the Invention

As used herein, the term "loweralkyl" means a linear or branched alkyl group with 1-8, preferably 1-4, carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, hexyl, and octyl. This definition also applies to a loweralkyl moiety in the loweralkoxy, loweralkylthio, and di(loweralkyl)amino groups. Thus, examples of loweralkoxy groups are methoxy, ethoxy, propoxy, sec-butoxy, and isohexoxy; examples of loweralkylthio groups are methylthio, ethylthio, tert-butylthio, and hexylthio; and examples of di(loweralkyl)amino groups are dimethylamino,

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diethylamino, diisopropylamino, di(*n*-butyl)amino, and dipentylamino.

The terms "halo" and "halogen" as used herein refers to a substituent which may be fluoro, chloro, 5 bromo, or iodo.

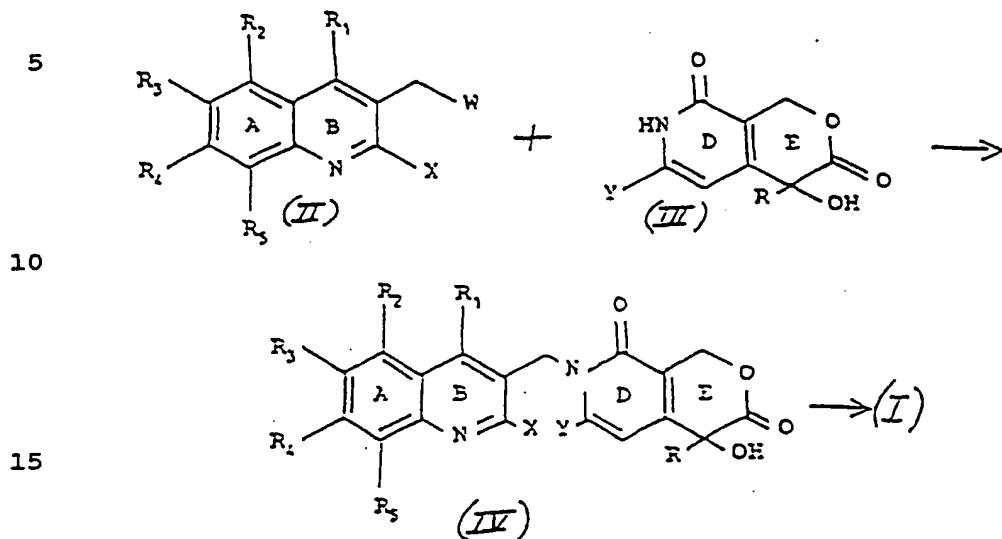
Substituents on the "A" ring of the compounds disclosed herein may be joined together to form a bifunctional substituent such as the methylenedioxy group. Methylenedioxy substituents may be bonded to 10 any two consecutive positions in the A ring, for example, the 9,10, the 10,11, or the 11,12 positions.

Substituents which are standard amino acids may be any of the twenty amino acids commonly found in naturally occurring proteins, and are well known in the 15 art. These provide a substituent of the formula -NHCHR₁COOH, with R being the side chain of any of the twenty standard amino acids. The amino acids may be of any configuration, but preferably have an (L) configuration.

A compound of Formula I is produced in accordance with Scheme A below by alkylating a pyridone of Formula III with a chloromethylquinoline of 20 Formula II to produce a compound of Formula IV, and then cyclizing the compound of Formula IV to yield the 25 compound of Formula I.

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Scheme A



In Scheme A: Y is H; R and R₁ through R₅ are as given in connection with Formula I above; X is halogen, preferably bromo or iodo; and W is halogen, preferably chloro.

The starting materials of Scheme A, the compounds of Formula II and III, are prepared in accordance with Schemes B and C, D, or E below.

The pyridone of Formula III may be alkylated with a halomethylquinoline of Formula II in a suitable solvent, such as a polar protic solvent (e.g. isopropyl alcohol, ethanol, methanol), an aprotic solvent (e.g., 30 1,2-dimethoxyethane, tetrahydrofuran, toluene, acetonitrile, or dimethylformamide) or alternatively in an aqueous solution in the presence of a phase transfer catalyst. The reaction is preferably carried out under mildly basic conditions, to minimize attack on the 35 pyridone ring oxygen. The reaction may be carried out as a single step, or may conveniently be carried out in two stages by, first, forming the anion of the pyridone

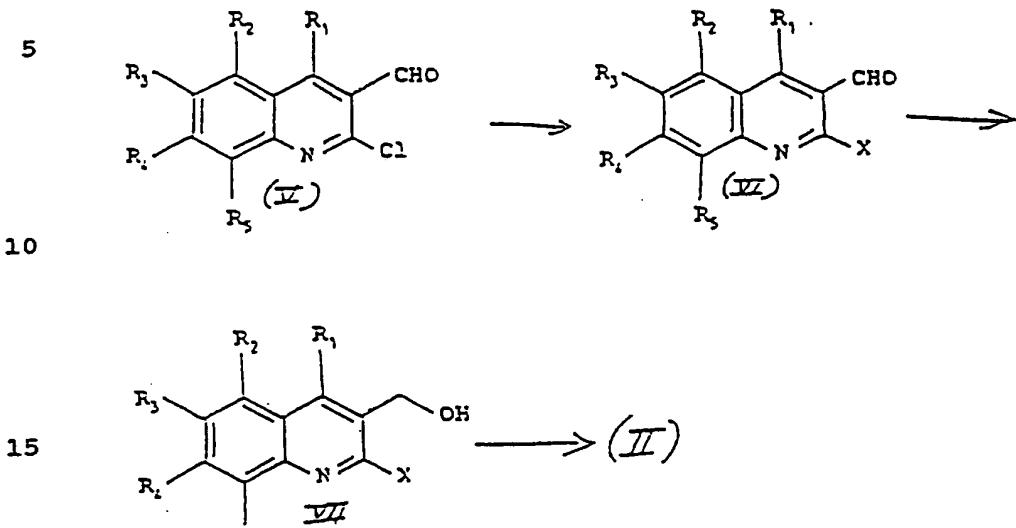
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by addition of an alkali earth salt (e.g., potassium tert-butoxide) at about room temperature, and then adding the halomethylquinoline to the reaction solution and heating the solution between about 60° to about
5 100° Centigrade for 4-24 hours.

The compound of Formula IV may be cyclized to yield the compound of Formula I by an intramolecular Heck reaction. The reaction is carried out in the presence of a palladium catalyst (e.g., palladium acetate) under basic conditions in a polar aprotic solvent such as acetonitrile or dimethylformamide. A phase transfer catalyst such as a tetraalkylammonium halide salt is preferably included. The reaction should be carried out in an inert atmosphere, such as under argon. The reaction mixture may be heated to a temperature between about 50° to about 100°C for about 1 to 24 hours. Variations on these conditions will be apparent from the literature on the Heck reaction.
See, e.g., R. Grigg et al. *Tetrahedron* 46, 4003-4008
20 (1990).

The compounds of Formula II may be prepared in accordance with Scheme B below, where R₁ through R₅ are as given in connection with Formula I above, and X is bromo or iodo, preferably iodo.

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Scheme B

20

The starting materials in Scheme B, the compounds of Formula V, are made by known techniques, such as by chlorination of a quinoline. See, e.g., *Progress in Heterocyclic Chemistry* 2, 180

25 (H. Suschitzky and E. Scriven eds. 1990). In the alternative, compounds of Formula V may be made from the substituted acetanilide as described by O. Meth-Cohn et al., *J. Chem. Soc. Perkin Trans. I* 1981, 1520.

The halo group on the carboxaldehyde of
30 Formula V is exchanged with an iodo or bromo (preferably iodo) to produce the carboxaldehyde of Formula VI. The exchange reaction may be carried out in acetonitrile in the presence of a catalytic amount of a strong acid, such as HCl, by heating the reaction mixture to between about 70° to about 90°C for at least about 4 hours.

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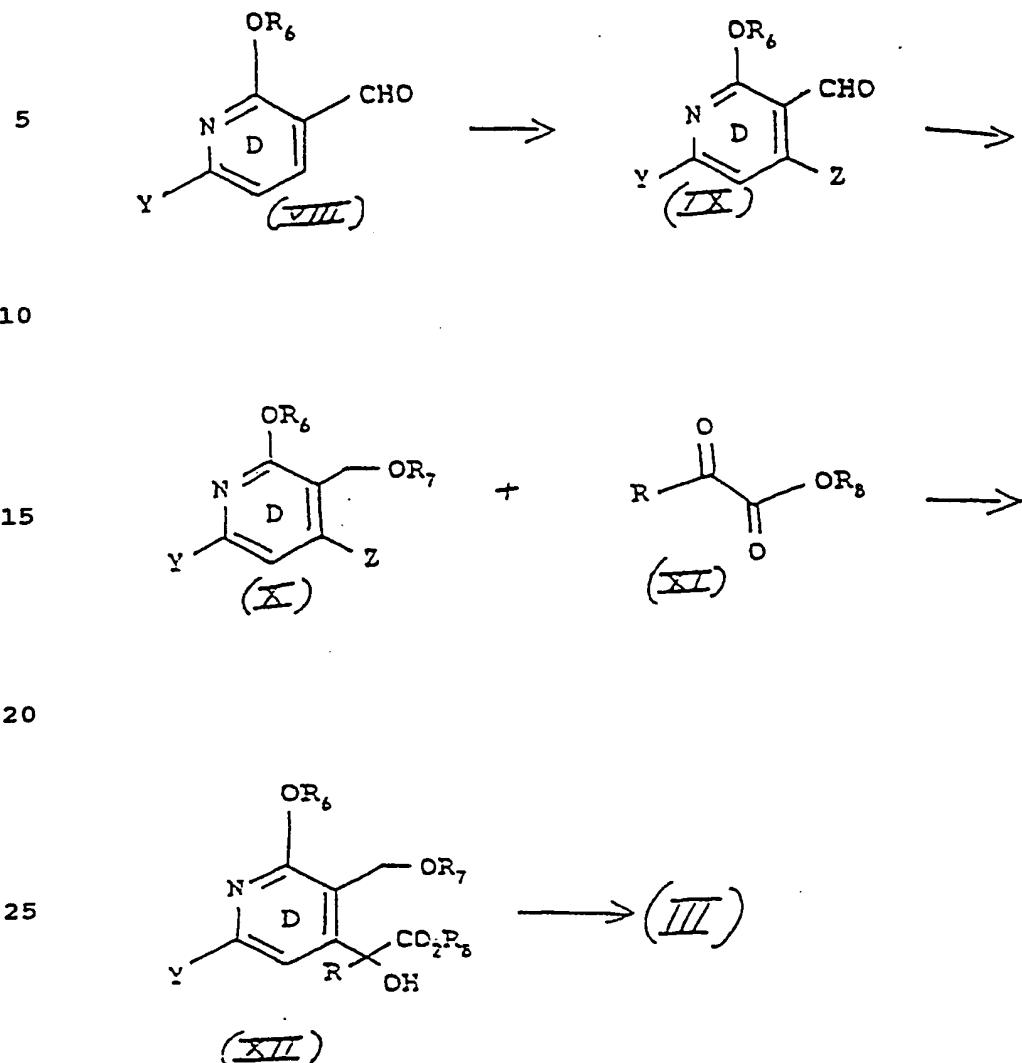
The carboxaldehyde of Formula VI is then reduced to produce the hydroxymethylquinoline of Formula VII. The reaction is carried out with a mild reducing agent to avoid reducing the quinoline ring, at 5 a temperature of from about 0° to about 25°C, in an alcohol solvent. An alternative route for producing a compound of Formula VII is disclosed in N. Narasimham et al., *J. Chem. Soc., Chem. Commun.*, 1985, 1368-1369.

A compound of Formula II is produced from the 10 hydroxymethylquinoline of Formula VII in accordance with conventional procedures in a solvent in which the reactants are soluble, such as dimethylformamide. The reaction is preferably carried out at lower temperatures to provide a higher yield.

15 The compounds of Formula III above are preferably prepared in accordance with Scheme C below, wherein R is as given in connection with Formula I above, R₆ and R₇ are loweralkyl, preferably methyl, R₈ is loweralkyl, preferably ethyl, Y is Cl or H, and Z is 20 halo, preferably bromo or iodo.

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Scheme C



The starting materials for Scheme C, the compounds of Formula VIII, may be prepared in accordance with known techniques. For example, the synthesis of 2-methoxy-3-pyridinecarboxaldehyde is disclosed in D. Comins and M. Killpack, *J. Org. Chem.* 55, 69-73 (1990).

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In Scheme C, the carboxaldehyde of Formula VIII is halogenated to produce the 4-halo-3-pyridinecarboxaldehyde of Formula IX. Halogenation at the 4- position may be carried out by reacting the 5 carboxaldehyde of Formula VIII with a lithiated diamine, such as lithiated N,N,N'-trimethylethylenediamine, in dimethoxyethane or tetrahydrofuran to protect the aldehyde and direct subsequent C-4 lithiation, and by then lithiating the 10 C-4 position of the pyridine with a suitable lithiating reagent, such as n-butyllithium. See D. Comins and M. Killpack, *supra*. The C-4 lithiated pyridine intermediate is preferably halogenated by adding the intermediate to a solution of iodine or bromine in a 15 polar or nonpolar organic solvent, preferably at a temperature of at least as low as about -70°C.

The compound of Formula IX is reduced in an alcoholic acidic media in the presence of a trialkylsilane to yield the alkoxymethylpyridine of 20 Formula X. The acid should be a strong acid, such as sulfuric or trifluoroacetic acid. At least about 2 molar equivalents of a suitable alcohol (e.g., methanol, ethanol, tert-butanol) should be included to convert the aldehyde to the ether. Reference may be 25 made to the literature on the silane reduction of aldehydes for conditions and variations on this reaction. See, e.g., M. Doyle et al., *J. Am. Chem. Soc.* 94:10, 3659-3661 (1972).

The compound of Formula X is lithiated at the 30 C-4 position with a lithiating agent such as n-butyllithium, and then reacted with a compound of Formula XI such as an alkyl α -ketobutyrate (e.g., methyl α -ketobutyrate, ethyl α -ketobutyrate, tert-butyla-ketobutyrate) to produce the compound of Formula 35 XII in essentially the manner described by R. Lyle et al., *J. Org. Chem.* 38, 3268-3271 (1973). The reaction may be carried out in a tetrahydrofuran or ether

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solvent at a temperature of at least as low as about - 50°C, with the alkyl α-ketobutyrate being added to the reaction solution as a single aliquot.

The compound of Formula XII is then cyclized
5 to yield the compound of Formula III. Cyclization may be carried out by reacting the compound of Formula XII with bromo- or iodo(trimethyl)silane (preferably iodo(trimethyl)silane) in a neutral or polar aprotic solvent such as acetonitrile, followed by reaction with
10 a strong acid solution to cleave the ethers and yield the compound of Formula III (the ring forming spontaneously upon cleavage of the ethers). The bromo- or iodo(trimethyl)silane is preferably generated in situ in accordance with known techniques, such as by the
15 reaction of chlorotrimethylsilane with a halogen salt or elemental halogen. See A. Schmidt, *Aldrichimica Acta* 14, 31-38 (1981).

When Y is halo in the compound of Formula III, the compound may be hydrogenated by any suitable
20 technique, preferably by catalytic hydrogenation in the presence of a palladium catalyst in a hydrogen atmosphere under pressure (e.g., at least three atmospheres). See generally J. March, *Advanced Organic Chemistry*, 510-511 (3d. Ed. 1985).

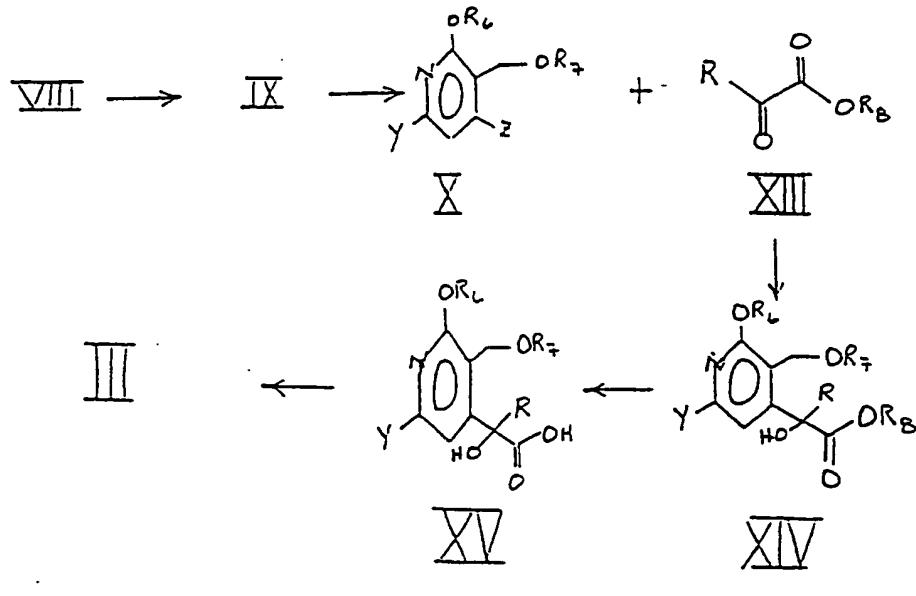
25 As alternatives to Scheme C, a compound of Formula III, where Y is H, may be prepared in the manner described in D. Comins, Ph.D. Thesis, University of New Hampshire, Durham, NH, at 25-29 (1977), and as described in Lyle et al., *J. Org. Chem.* 38, 3268-3271
30 (1973).

Another alternative to Scheme C is Scheme D, shown below,

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Scheme D

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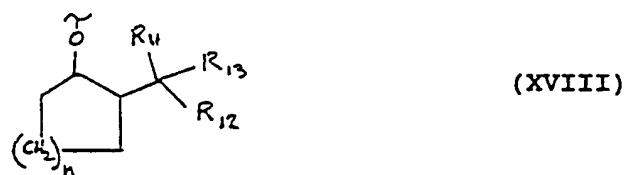
25 wherein R, R_6 , R_7 , Y, and Z are as given in connection
 with Formula III above. R_8 can be any chiral moiety
 which, because of its geometric configuration, directs
 the nucleophilic substitution of compound XIII by
 compound X to preferentially form the tertiary alcohol
 30 of compound XIV in one stereochemical orientation over
 its opposite stereochemical orientation. R_8 forces a
 preferential orientation of compound XIV by sterically
 hindering the formation of the non-preferred
 diastereomer. Exemplary chiral compounds suitable for
 35 use in the process include aryl and alkyl aryl
 compounds optionally substituted from 1 to 5 times with
 C1-C4 alkyl groups, any of the compounds disclosed in

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U.S. Patent Application Serial No. 07/855,721, the subject matter of which is herein incorporated by reference, 4-phenylmethyl -2 oxazolidine, 3-(1-naphthyl)-4,7,7-trimethylbicyclo [2.2.1] heptane, 5 trans-2,5 Bis(methoxymethoxy methyl)pyrrolidine, 2,10-camphorsulfamide, N,N- dicetylhexyl-10-camphorsulfamide, proline benzyl ester, pantolactone, and 4-benzyl-2-oxazolidinone. Preferred chiral auxiliaries are compounds of the Formula XVIII

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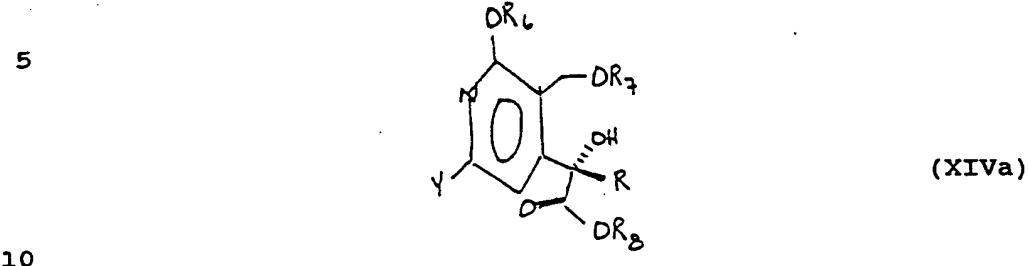
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wherein n is 1, 2, or 3, R_{11} is C1-C4 alkyl, R_{12} is the same C1-C4 alkyl group as R_{11} , or R_{11} and R_{12} together form cyclopentane or cyclohexane, and R_{13} is selected from the group consisting of phenyl, naphthyl, anthryl, or phenanthryl optionally substituted from 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl groups. The position of alkyl substituents on the aryl group is not critical; for example, phenyl can be substituted at positions 1-6, naphthyl from positions 1-8, anthryl from positions 1-10, and phenanthryl from positions 1-10 substituted from 1 to 5 times with C1-C4 alkyl groups. It is understood that the oxygen atom illustrated in XVIII links the chiral auxiliary to the carbonyl carbon of compound XIII and is included in the Formula XVIII to indicate the preferred bonding position of the cyclic alkyl group that carbonyl carbon. In a more preferred chiral auxiliary, R_{11} and R_{12} are both methyl or ethyl, and R_{13} is phenyl.

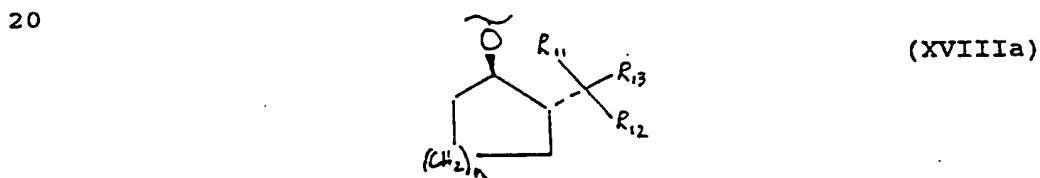
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In many instances it will be desirable that compound XIV has the stereochemical orientation of Formula (XIVa).



In such instances, R₈ should be an optically pure chiral auxiliary that will permit only the formation of diastereomers of compound XIV having this orientation.

15 As used herein, an "optically pure" compound is one which contains at least 99 percent of one enantiomer of that compound. Preferred chiral auxiliaries for forming the diastereomers of Formula XIVa are as shown in Formula XVIIIA



25 wherein R, R₁₁, R₁₂, and R₁₃ are as defined for Formula VIII. As above, the oxygen atom of compound XVIIIA is included to show bonding position on the cyclic alkyl group and stereochemical orientation of the substituents thereon.

30 Scheme D proceeds in the same manner as Scheme C through the synthesis of compound X. At that point compound X is dehalogenated with a base of the formula A⁺B⁻, wherein A⁺ is an inorganic cation, and B⁻ is an organic anion, to form an intermediate, then 35 reacting that intermediate with an α -ketoester of Formula XIII to form a compound of Formula XIV.

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The base A⁺B⁻ can be any combination of an inorganic cation and an organic anion which will remove Z from compound X to form a reactive carbanion intermediate. Exemplary inorganic cations include 5 sodium, potassium, and lithium, with lithium being more preferred. The organic anion can be any anion which is sufficiently basic to remove substituent Z from compound X but is insufficiently strong to remove substituent Y from compound X. Exemplary organic 10 anions include propyl, n-butyl, t-butyl, phenyl, and n-pentyl, with n-butyl being preferred.

The reaction step in which Z is removed from compound X can be carried out through the use of standard conditions for removing halogens from aromatic 15 compounds. Preferably, this step is carried out in an inert atmosphere, such as argon or nitrogen, and in an aprotic solvent, such as tetrahydrofuran, diethyl ether, dimethoxyethane, and toluene, with tetrahydrofuran being preferred. The reaction is 20 preferably carried out at a reduced temperature, and more preferably is carried out at below 0°C.

The combination of the intermediate produced by reaction with base A⁺B⁻ and the α -ketoester of formula XIV can be carried out through the use of 25 standard conditions for nucleophilic attack of an aromatic carbanion at an α -carbonyl carbon. Preferably, the reaction is carried out in an aprotic solvent, such as those listed above, with tetrahydrofuran being preferred, and is carried out at 30 a reduced temperature, preferably below 0°C. In a more preferred embodiment of the process, the reacting step and the combining step are carried out in the same reaction vessel, i.e., in situ.

Proceeding stepwise through Scheme D, a 35 compound of Formula XV can then be prepared by saponifying a compound of Formula XIV with a base to

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form an intermediate, then protonating the intermediate with aqueous acid.

The saponification step can be carried out under any conditions that are known for saponifying esters to carboxylic acids. Preferably, the saponifying base used is a mixture of an inorganic base, such as sodium hydroxide or potassium hydroxide, and a relatively polar organic solvent, such as ethanol. The protonating step can be carried out with any aqueous acid solution, such as hydrochloric or sulfuric acid, that will protonate the carboxylate anion resulting from saponification of the ester linkage of compound XIV.

Preferably, the process is carried out so that after the saponification step, but prior to the protonating step, the chiral auxiliary (R_8) can be recovered in good yield for re-use. This can be performed by any method of recovery known to be suitable for compounds of this type. Preferably, the basic solution remaining from the saponification is washed with a non-polar, aprotic solvent, such as dimethyl ether or diethyl ether, which extracts the chiral auxiliary R_8 from solution.

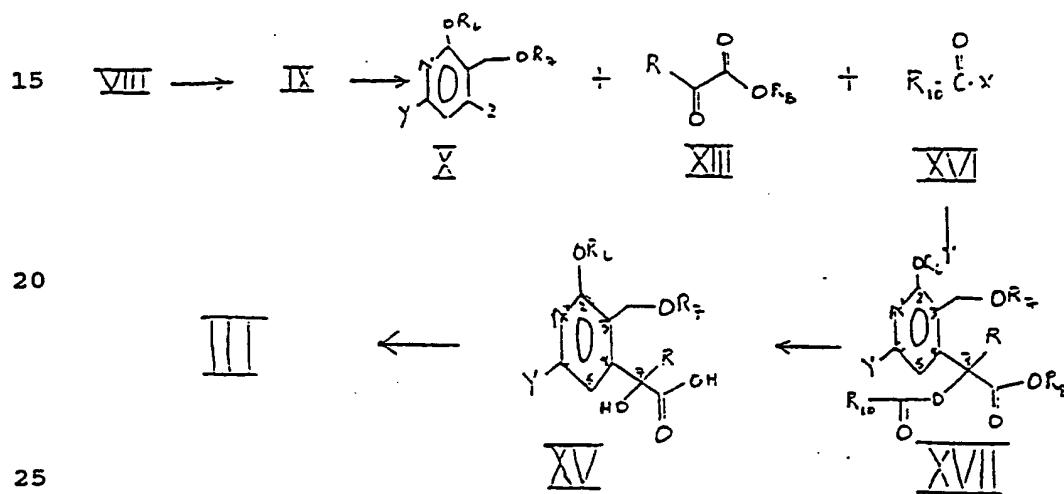
The final step of Scheme D is the formation of Compound III from a compound of Formula XV. This process comprises the steps of reacting compound of Formula XV with a halotrialkylsilane in the presence of an alkyl or aryl amine to form an intermediate, then cyclizing the intermediate by hydrolysis of the reaction product in aqueous acid to cleave the ether linkage of R_6 and R_7 , the ring forming spontaneously upon ether cleavage. A preferred halotrialkylsilane is iodotrimethylsilane. Exemplary amines are secondary and tertiary amines, with 1,8-diazabicyclo[5.4.0]undec-7-ene being preferred. The ethers can be cleaved by conventional methods, such as those described above in Scheme C for producing compound III from compound XII.

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The process is preferably carried out in an aprotic solvent, such as acetonitrile, tetrahydrofuran, or diethylether. Also, the process is preferably conducted so that the reacting step and the cyclizing 5 step are carried out in the same reaction vessel, i.e., in situ.

Alternatively, a compound of the Formula XV can be made by Scheme E from a compound of Formula X. Scheme E is shown below.

10

Scheme E

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R , R_6 , R_7 , and R_8 are as given above for Scheme D. R_{10} can be any aryl, alkyl, or alkyl aryl group which will cause the compound of Formula XVII to recrystallize and separate from the undesired minor 35 diastereomer. R_{10} is preferably selected from the group consisting of biphenyl, anthryl, phenanthryl, and phenyl, any of which can be substituted from 1 to 5

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times with C1-C4 alkyl groups. The position of alkyl substituents on the aryl group is not critical; for example, phenyl can be substituted at positions 1-6, naphthyl from positions 1-8, anthryl from positions 1-10, and phenanthryl from positions 1-10 substituted from 1 to 5 times with C1-C4 alkyl groups. More preferably, R₁₀ is biphenyl. X is selected from the group consisting of chlorine, bromine, and iodine.

Scheme E represents a process comprising the steps of reacting a compound of Formula X with a base A*B' to form first intermediate, combining the intermediate with an α-ketoester containing a chiral auxiliary of Formula XIII to form a second intermediate, the alkoxide of compound XIV, then acylating this second intermediate with a compound of Formula XVI to form a compound of Formula XVII.

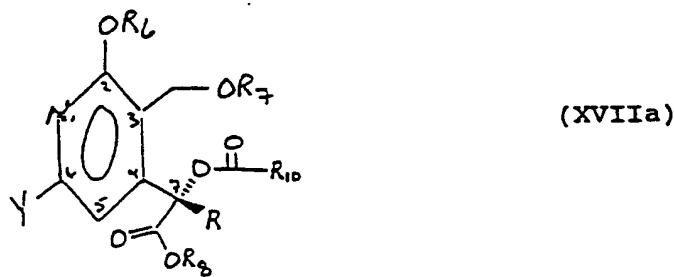
This scheme differs from Scheme D only in that another acylation step is included for the formation of an additional ester linkage at the hydroxyl group attached to the chiral carbon at position 7. The purpose of the additional substituent R₁₀ is to form a compound that can be separated easily from solution by recrystallization. Without this step, it can be difficult to separate the compound of Formula XIV from a minor diastereomer by-product of the reaction; this is problematic if, as is often the case when chiral auxiliaries are used in synthetic reactions, a diastereomerically or optically pure product is desired. By including in compound XVII the ester linking R₁₀ to compound XIV, the reaction product XVII can be purified by standard recrystallization methods, such as precipitation from an organic solvent, to produce a diastereomerically pure compound XVII. As used herein, "diastereomerically pure" means that a compound sample comprises at least 99 percent of one of at least two possible diastereomers. This diastereomerically pure compound XVII can in turn be

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used to produce an optically pure compound XV, which in turn can be used to produce an optically pure compound III.

Scheme E proceeds in the manner described above in Scheme D for the preparation of Compound XIV. Once compound XIV has been prepared, the acylation step can be carried out in any manner known for acylating tertiary alcohols with acyl halides. In a preferred embodiment, R₁₀ is added to a reaction mixture in which compound XIV has been prepared in its alkoxide form, so that the reaction proceeds *in situ*. The solvent should be an aprotic solvent, such as tetrahydrofuran, diethyl ether, dimethoxyethane, or toluene, with tetrahydrofuran being preferred. Preferably the reaction occurs in an inert atmosphere, such as under argon or nitrogen. The reaction product is separated from the reaction mixture, preferably by recrystallization, for use in subsequent steps. If an optically pure chiral axillary R₈ was used, the recrystallized compound XVII will contain only one disastereomer, the diastereomer having a stereochemical orientation of the substituents of the chiral carbon 7 of compound XVII directed by the chiral auxiliary. A preferred orientation at chiral carbon atom 7 is shown in Formula XVIIa.

30



35 which can be produced by use of an optically pure compound of Formula XIIIa. Any further synthetic process that includes compound XVIIa will then produce

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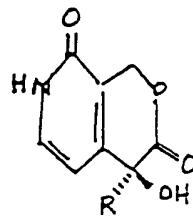
reaction products having the same stereochemical orientation at chiral carbon 7.

From this point, Scheme E parallels Scheme D. Compound XVII is saponified with a base to form an intermediate, then the intermediate is protonated to form a compound of Formula XV. As was true for the saponifying step of Scheme D, this step of Scheme E can be carried out with any base that will cleave the ester linkages bonding R₈ and R₁₀ to compound XVII.

Preferably, the base is a mixture of a relatively polar organic solvent, such as ethanol, and an inorganic aqueous base, such as sodium hydroxide. After the saponifying base cleaves both ester linkages present in compound XVII to form the carboxylate and alkoxide form of the compound, the protonating acid then protonates these functional groups to form a compound of Formula XV. As in Scheme D, the chiral auxiliary can be recovered after saponification for re-use by nonpolar solvent washing or some other suitable technique.

The final step of Scheme E is the cyclizing of compound XV to compound III. The same reaction conditions listed above for Scheme D are suitable here. As indicated above, the compound can be made in an optically pure form by using an optically pure chiral auxiliary R₈ in Scheme E; a preferred stereochemical orientation is shown in Formula IIIa,

30



(IIIa)

which can be made from the diastereomerically pure form of compound XVIIa after saponification to an optically pure form of compound Xva.

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Specific examples of compounds which may be prepared by the method of the present invention include 9-methoxy-camptotheclin, 9-hydroxy-camptotheclin, 9-nitro-camptotheclin, 9-amino-camptotheclin, 10-hydroxy-
5 camptotheclin, 10-nitro-camptotheclin, 10-amino-camptotheclin, 10-chloro-camptotheclin, 10-methyl-camptotheclin, 11-methoxy-camptotheclin, 11-hydroxy-camptotheclin, 11-nitro-camptotheclin, 11-amino-camptotheclin, 11-formyl-camptotheclin, 11-cyano-
10 camptotheclin, 12-methoxy-camptotheclin, 12-hydroxy-camptotheclin, 12-nitro-camptotheclin, 10,11-dihydroxy-camptotheclin, 10,11-dimethoxy-camptotheclin, 7-methyl-10-fluoro-camptotheclin, 7-methyl-10-chloro-camptotheclin, 7-methyl-9,12-dimethoxy-camptotheclin,
15 9,10,11-trimethoxy-camptotheclin, 10,11-methylenedioxy-camptotheclin and 9,10,11,12-tetramethyl-camptotheclin.

Compounds of Formula I have antitumor and antileukemic activity. Additionally, compounds of Formula I wherein R₁ is halo are useful as intermediates
20 for, among other things, making compounds of Formula I wherein R₁ is loweralkyl.

Those skilled in the art will appreciate that additional changes can be made in the compounds of Formula I (see, for examples, J. Cai and C. Hutchinson,
25 supra), which changes will not adversely affect the new processes disclosed herein and do not depart from the concept of the present invention.

In the Examples which follow, "mg" means milligrams, "g" means grams, "M" means Molar, mL means
30 millimeter(s), "mmol" means millimole(s), "Bu" means butyl, "THF" means tetrahydrofuran, "h" means hours, "min" means minutes, "C" means Centigrade, "p.s.i." means pounds per square inch, "DMF" means dimethylformamide, "TLC" means thin layer
35 chromatography, and "PLC" means preparative thin layer chromatography.

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EXAMPLE 1

6-Chloro-2-methoxy-3-pyridinecarboxaldehyde

To a solution of tert-butyllithium (1.7 M in pentane, 48.5 mL, 83.0 mmol) in 150 mL of THF at -78°C 5 was added 6-chloro-2-methoxypyridine (8.94 mL, 75.0 mmol) over 5 min. The reaction mixture was stirred at -78°C for 1 h, then dimethylformamide (7.55 mL, 97 mmol) was added and the mixture was stirred at this temperature for 1.5 h. After the addition of glacial 10 acetic acid (8.6 mL, 150 mmol), the reaction mixture was allowed to warm to room temperature over a 30- min period, then diluted with ether (200 mL). The organic phase was washed with saturated aqueous NaHCO₃ (100 mL) and brine (100 mL), and was dried over MgSO₄. 15 Concentration afforded the crude product as a light yellow solid which was recrystallized from hexanes to give 9.6 g (75%) of 6-chloro-2-methoxy-3-pyridinecarboxaldehyde as a white solid: mp 80-81°C (mp 62-64°C) (See Dainter, R.S.; Suschitzky, H.; 20 Wakefield, B.J. Tetrahedron Lett. 1984, 25, 5693.). ¹H NMR (300 MHz, CDCl₃) δ 10.31 (s, 1H), 8.07 (d, 1H, J = 9 Hz), 7.03 (d, 1H, J = 9 Hz), 4.09 (s, 3H); IR (nujol) 1685, 1580, 1565, 1270, 1140, 1090, 1005, 905, 820, 755 cm⁻¹.

25

EXAMPLE 2

6-Chloro-4-iodo-2-methoxy-3-pyridinecarboxaldehyde

To a solution of N,N,N',N'-trimethyl- 30 ethylenediamine (2.46 mL, 19.23 mmol) in 15 mL of 1,2-dimethoxyethane at - 23°C was added n-BuLi (9.22 mL, 19.23 mmol), and the solution was stirred at -23°C for 20 min. The mixture was transferred using a double-tipped needle to a solution of 6-chloro-2-methoxy-3-pyridinecarboxaldehyde (3.0 g, 17.5 mmol) in 40 mL of 35 1,2-dimethoxyethane at - 23°C. After stirring for 15 min, n-BuLi (12.6 mL, 26.2 mmol) was added and the dark mixture was stirred an additional 2 h at -23°C. The

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solution was transferred using a double-tipped needle to a solution of iodine (8.04 g, 31.7 mmol) in 40 mL of 1,2-dimethoxyethane at -78°C. After stirring at -78°C for 30 min, the cooling bath was removed and the
5 reaction mixture was allowed to warm for 20 min, then quenched with water. The mixture was extracted with ether (2 x 30 mL) and the combined organic layers were washed successively with 30-mL portions of 10% aqueous Na₂S₂O₃, water and brine, and dried over MgSO₄.
10 Concentration afforded 4.62 g (89%) of crude product to which was added 50 mL of hexanes. The mixture was stirred and allowed to stand at 5°C overnight. Filtration gave 2.67 g of 6-chloro-4-iodo-2-methoxy-3-pyridinecarboxaldehyde as a yellow solid: mp 120-124°C. Concentration of the hexane washings and
15 purification of the residue by radial preparative thin-layer chromatography (silica gel, 5% ethyl acetate/hexanes) gave an additional 1.41 g of product (mp 120-124°C), raising the total yield of the compound
20 to 78%. Recrystallization from hexanes gave an analytical sample as a bright yellow solid: mp 129-130°C. ¹H NMR (300 MHz, CDCl₃) δ 10.16 (s, 1H), 7.59 (s, 1H), 4.07 (s, 1H); IR (nujol) 1690, 1350, 1260, 1095, 1010, 900, 840 cm⁻¹.

25

EXAMPLE 3

2-Chloro-4-iodo-6-methoxy-5-(methoxymethyl)pyridine

To a mixture of 6-chloro-4-iodo-2-methoxy-3-pyridinecarboxaldehyde (1.07 g, 3.60 mmol),
30 triethylsilane (0.86 mL, 5.40 mmol) and methanol (0.43 mL, 10.6 mmol) at 0°C was added trifluoroacetic acid (2.2 mL, 28.6 mmol), and the resulting solution was stirred at 25°C for 14 h. After dilution with ether (30mL), saturated NaHCO₃ was added until the aqueous
35 phase was rendered basic. The aqueous layer was extracted with ether (10mL), and the combined ether layers were washed with water (10mL) and brine (10 mL),

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and dried (Na_2SO_4). Concentration gave the crude product which was purified by radial PLC (silica gel, 5% ethyl acetate/hexanes) to afford 2-chloro-4-iodo-6-methoxy-5-(methoxymethyl)pyridine as a white solid
5 (1.05 g, 93%): mp 69-72°C. Recrystallization from hexanes provided an analytical sample: mp 74-75°C. ^1H NMR (300 MHz, CDCl_3) δ 7.40 (s, 1H), 4.53 (s, 2H), 3.96 (s, 3H), 3.42 (s, 3H); IR (nujol) 1550, 1300, 1115, 1090, 1020, 940, 905, 830, 720 cm^{-1} .

10

EXAMPLE 4

Ethyl 2-hydroxy-2-(6'-chloro-2'-methoxy-3'-methoxymethyl-4'-pyridyl)butyrate

To a solution of 2-chloro-4-iodo-6-methoxy-5-(methoxymethyl)pyridine (2.28 g, 7.30 mmol) in 50 mL of THF at -90°C was added n-BuLi (3.46 mL, 8.03 mmol) over 15 5 min and the resulting solution was stirred at -90°C for 30 min. Ethyl α -ketobutyrate (1.25 mL, 9.45 mmol) was added, the reaction mixture was stirred at -90°C 20 for 30 min, then allowed to warm at ambient for 20 min, and quenched with saturated NH_4Cl . After removal of most of the solvent under reduced pressure, the residue 25 was taken up in 40 mL of ether, washed with dilute NaHCO_3 (15 mL) and brine (15 mL), and was dried over MgSO_4 . Evaporation of the solvent in vacuo and purification of the residue by radial PLC (10% acetone/hexanes) afforded ethyl-2-hydroxy-2-(6'-chloro-2'-methoxy-3'-methoxymethyl-4'-pyridyl)butyrate (1.53 g, 66%) as a light yellow, viscous oil. ^1H NMR (300 30 MHz, CDCl_3) δ 7.07 (s, 1H), 4.75 (d, 1H, $J = 12$ Hz), 4.47 (d, 1H, $J = 12$ Hz), 4.24 (q, 1H, $J = 6$ Hz), 4.17 (q, 1H, $J = 6$ Hz), 3.96 (s, 3H), 3.37 (s, 3H), 2.16 (m, 2H), 1.24 (t, 3H, $J = 6$ Hz); IR (film) 3400, 1735, 1580, 1555, 1305, 1235, 1130, 1090, 1020, 905, 830, 730 35 cm^{-1} .

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EXAMPLE 5

9-Chloro-7-oxopyrido[5,4-c]-2-
oxo-3-ethyl-3-hydroxy-3,6-dihydropyran

To a stirred mixture of the hydroxy ester
5 prepared in Example 4 above (1.53 g, 4.82 mmol) and
sodium iodide (2.89 g, 19.3 mmol) in dry CH₃CN (35 mL)
at 25°C was added dropwise chlorotrimethylsilane (2.45
mL, 19.3 mmol). The resulting solution was heated at
reflux for 4 h, the solvent was removed under reduced
10 pressure, and 100 mL of 5N HCl was added to the
residue. After heating at a gentle reflux for 4 h, the
mixture was stirred at 25°C overnight, then extracted
with six 30-mL portions of CHCl₃, containing 5% CH₃OH.
The combined organic extracts were washed with 40 mL of
15 half-saturated NaCl containing Na₂S₂O₃, followed by 40
mL of saturated NaCl. After drying over Na₂SO₄, the
solvent was removed under reduced pressure and the
residue was purified by radial PLC (silica gel, 5%
CH₃OH/CHCl₃) to give 9-chloro-7-oxopyrido[5,4-c]-2-oxo-
20 3-ethyl-3-hydroxy-3,6-dihydropyran (743 mg, 63%) as an
off-white solid: mp 205-207°C. Recrystallization from
CHCl₃/CH₃OH gave an analytically pure sample as a white
solid: mp 207-208°C. ¹H NMR (300 MHz, CDCl₃, DMSO-d6) δ =
6.79 (s, 1H), 5.49 (d, 1H, J = 15 Hz), 5.13 (d, 1H, J =
25 15 Hz), 1.78 (q, 2H, J = 6 Hz), 0.93 (t, 3H, J = 9 Hz),
IR (nujol) 3450, 1740, 1640, 1600, 1560, 1320, 1225,
1140, 1035, 995, 940 cm⁻¹.

EXAMPLE 6

7-Oxopyrido[5,4-c]-2-oxo-
3-ethyl-3-hydroxy-3,6-dihydropyran

A mixture of the chloropyridone prepared in
Example 5 above (400 mg, 1.64 mmol) and sodium acetate
(400 mg, 4.86 mmol) in 25 mL of ethanol was
35 hydrogenated over 10% Pd/C (100 mg) at 42 psi for 4 h.
The mixture was filtered through celite and the solids
were washed with CH₃OH. The filtrate was concentrated

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and the residue was purified by radial PLC (silica gel, 5% CH₃OH/CHCl₃) to give the pure product (256 mg, 75%) as a white solid: mp 230-232°C (dec.).

Recrystallization from CHCl₃/CH₃OH afforded an

5 analytical sample: mp 232°C (dec.). ¹H NMR (300 MHz, CHCl₃/DMSO-d6) δ 7.30 (d, 1H, J = 6 Hz), 6.49 (d, 1H, J = 6 Hz), 5.42 (d, 1H, J = 18 Hz), 5.12 (d, 1H, J = 18 Hz), 1.79 (m, 2H), 0.91 (t, 3H, J = 6 Hz); IR (nujol) 3300, 1750, 1640, 1620, 1555, 1065, 1030, 995, 805 cm⁻¹.

10

EXAMPLE 7

2-Chloro-3-quinolinecarboxaldehyde

To a solution of 0.46 mL (3.30 mmol) of diisopropylamine in 8 mL of THF at 0°C was added 1.53 mL (3.30 mmol) of n-BuLi dropwise. After 20 min the 15 solution was cooled to -78°C and 2-chloroquinoline (491 mg, 3.0 mmol) was added neat. The mixture was stirred at -78°C for 30 min, then dimethylformamide (0.39 mL, 5.04 mmol) was added dropwise and the reaction mixture 20 was stirred an additional 30 min at this temperature. After quenching at -78°C with glacial acetic acid (1 mL), the mixture was warmed to room temperature and diluted with ether (30 mL). The organic phase was washed with saturated NaHCO₃ solution (10 mL) and brine (10 mL), and was dried over MgSO₄. Concentration 25 afforded 2-chloro-3-quinolinecarboxaldehyde (530 mg, 92%) as a light yellow solid (mp 145-149°C), which was used directly in the next step without further purification. Recrystallization from ethyl acetate 30 afforded the pure compound as light yellow needles: mp 149-150°C (mp 148-149°C reported in Meth-Cohn, O.; Narhe, B.; Tarnowski, B. J. Chem. Soc. Perkin Trans. I 1981, 1520.). ¹H NMR (300 MHz, CDCl₃) δ 10.57 (s, 1H), 8.77 (s, 1H), 8.08 (d, 1H, J = 9 Hz), 8.0 (d, 1H, J = 9 Hz), 7.90 (t, 1H, J = 9 Hz), 7.67 (t, 1H, J = 9 Hz); IR (nujol) 1685, 1575, 1045, 760, 745 cm⁻¹.

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EXAMPLE 8

Preparation of 2-Chloro-3-quinoline-
carboxaldehyde from acetanilide

Following a literature procedure (see Meth-
5 Cohn, O.; Narhe, B.; Tarnowski, B. J. Chem. Soc. Perkin
Trans. I 1981, 1520), a phosphorus oxychloride (24.0
mL, 260 mmol) was added dropwise to an ice-cold
solution of dimethylformamide (7.20 mL, 93.0 mmol) and
the deep-red solution was stirred at 0°C for 30 min.
10 Acetanilide (5.0 g, 37.0 mmol) was added neat and the
mixture was stirred at 0°C for 30 min., then heated at
75°C for 16 h. The cooled mixture was poured into 250
mL of ice-water and stirred at 0-5°C for 30 min. The
product was filtered, washed with water, and
15 recrystallized from ethyl acetate to give 5.2 g (74%)
of 2-chloro-3-quinoline-carboxaldehyde as a light
yellow solid: mp 147-149°C.

EXAMPLE 9

20 2-Iodo-3-quinolinecarboxaldehyde
A mixture of the aldehyde prepared in
accordance with Example 7 or 8 above (5.0 g, 26.2
mmol), sodium iodide (10.0 g, 66.7 mmol) and
concentrated HCl (1 mL) in 100 mL of CH₃CN was heated at
25 reflux for 4.5 h. After removal of most of the solvent
in vacuo, aqueous Na₂CO₃ was added until the mixture was
basic, and the product was filtered and washed with
water. The crude product was recrystallized from 95%
ethanol to give 6.51 g (88%) of 2-iodo-3-
30 quinolinecarboxaldehyde as off-white fluffy needles:
mp 156-157°C (mp 150-152°C reported in Meth-Cohn, O.;
Narhe, B.; Tranowski, B.; Hayes, R.; Keyzad, A.;
Rhavati, S.; Robinson, A. J. Chem. Soc. Perkin Trans. I
1981, 2509). ¹H NMR (300 MHz, CDCl₃) δ 10.29 (s, 1H),
35 8.57 (s, 1H), 8.12 (d, 1H, J = 9 Hz), 7.98 (d, 1H, J =
9 Hz) 7.88 (t, 1H, J = 9 Hz), 7.68 (t, 1H, J = 9 Hz);

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IR (nujol) 1680, 1610, 1570, 1555, 1315, 1020, 1005,
750, 740 cm⁻¹.

EXAMPLE 10

5 3-Hydroxymethyl-2-iodoquinoline
To a stirred solution of 2-iodo-3-
quinolinecarboxaldehyde (595 mg, 2.10 mmol) in 40 mL of
CH₃OH at 0°C was added NaBH₄ (86 mg, 2.31 mmol), and the
mixture was stirred at 0°C for 30 min. After
10 concentrating the mixture to approximately one-half of
its original volume, water (30 mL) was added and the
mixture was allowed to stand at 5°C overnight. The
solids were filtered and the crude product (570) mg,
95% was recrystallized from methanol to give 3-
15 hydroxymethyl-2-iodoquinoline (505 mg, 84%) as
colorless needles: mp 189-190°C. ¹H NMR (300 MHz,
CDCl₃) δ 8.19 (s, 1H), 7.99 (d, 1H, J = 9 Hz), 7.87 (d,
1H, J = 9 Hz), 7.68 (m, 1H), 7.58 (t, 1H, J = 9 Hz),
5.45 (t, 1H, J = 6 Hz), 4.66 (d, 2H, J = 6 Hz); IR
20 (nujol) 3350, 1580, 1320, 1125, 1060, 995, 755, 720,
cm⁻¹.

EXAMPLE 11

25 3-Chloromethyl-2-iodoquinoline
To a stirred mixture of 3-hydroxymethyl-2-
iodoquinoline prepared in accordance with Example 10
above (350 mg, 1.23 mmol) and triphenylphosphine (483
mg, 1.84 mmol) in 10 mL of dry DMF at -23°C was added
N-chlorosuccinimide (246 mg, 1.84 mmol), and the
30 mixture was stirred for 1 h at -23°C. After the
addition of 40 mL of dilute aqueous NaHCO₃, the mixture
was extracted with ethyl acetate (20 mL) and then ether
(2x 15 mL). The combined organic extracts were washed
successively with 20-mL portions of dilute NaHCO₃, water
35 and brine, and were dried over MgSO₄. Concentration and
purification of the residue by radial PLC (silica gel,
10% ethyl acetate/hexanes) afforded 312 mg (84%) of 3-

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chloromethyl-2-iodoquinoline as a white crystalline solid: mp 138-140°C. Recrystallization from hexanes afforded an analytical sample as colorless needles: mp 139-140°C. ¹H NMR (300 MHz, CDCl₃) δ 8.17 (s, 1H), 8.07 (d, 1H, J = 9 Hz), 7.84 (d, 1H, J = 9 Hz), 7.75 (t, 1H, J = 9 Hz), 7.62 (t, 1H, J = 9 Hz), 4.80 (s, 1H); IR (nujol) 1585, 1555, 1260, 1010, 780, 755, 710 cm⁻¹.

EXAMPLE 12

10 8-(21-Iodo-3'-quinolylmethyl)-7-oxopyrido[5,4-c]-2-
 oxo-3-ethyl-3-hydroxy-3, 6-dihydropyran

To a solution containing 45 mg (0.40 mmol) of potassium tert-butoxide in 4 mL of dry isopropyl alcohol at 25°C was added 55 mg (0.26 mmol) of 7-oxopyrido[5,4-c]-2-oxo-3-ethyl-3-hydroxy-3, 6-dihydropyran prepared in accordance with Example 6 above and the mixture was stirred at 25°C for 30 min. A solution of 3-chloromethyl-2-iodoquinoline prepared in accordance with Example 11 above (104 mg, 0.35 mmol) in 1 mL of CH₃OH was added dropwise to the white suspension, and the resulting solution was heated at 75°C for 24 h. After quenching the reaction mixture with saturated NH₄Cl, the solvents were removed under reduced pressure, and the residue was taken up in CH₂Cl₂ (20 mL) and washed with brine (2 × 10 mL). Concentration and purification of the residue by radial PLC (2% CH₃OH/CHCl₃) gave the product (99 mg, 80%) as a white solid: mp 171-174°C (dec.). Recrystallization from ethyl acetate/hexanes afforded an analytical sample: mp 174°C (dec.). ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, 1H, J = 9 Hz), 7.70-7.80 (m, 3H), 7.55-7.61 (m, 2H), 6.61 (d, 1H, J = 9 Hz), 5.63 (d, 1H, J = 15 Hz), 5.43 (d, 1H, J = 15 Hz), 5.27 (d, 1H, J = 9 Hz), 5.22 (d, 1H, J = 9 Hz); IR (nujol) 3350, 1750, 1650, 1590, 1565, 1160, 1140, 1000, 750 cm⁻¹.

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EXAMPLE 13

(±)-Camptothecin

A mixture of 8-(2'-ido-3'-quinolylmethyl)-7-oxopyrido[5,4-c]-2-oxo-3-ethyl-3-hydroxy-3,6-

5 dihydropyran prepared in accordance with Example 12 above (76 mg, 0.16 mmol), K₂CO₃ (44 mg, 0.32 mmol), tetrabutylammonium bromide (52 mg, 0.16 mmol) and Pd(OAc)₂ (3.6 mg, 0.016 mmol) in 15 mL of dry acetonitrile under argon was heated at 90°C for 5 h.

10 TLC analysis of the reaction mixture showed a single spot which was highly U.V. active. The mixture was cooled, concentrated, and the residue was taken up in 30 mL of CHCl₃ containing 10% CH₃OH. This was washed with two 10-mL portions of saturated aqueous NH₄Cl. The 15 organic layer was dried over Na₂SO₄ and concentrated. The dark residue was subjected to radial PLC (silica gel, 4% CH₃OH/CHCl₃), to give 17 mg of an orange solid which was shown by NMR analysis to be a mixture of impure (±)-camptothecin and tetrabutylammonium bromide.

20 The aqueous washings were filtered to give a yellow solid which was purified by radial PLC (silica gel, 4% CH₃OH/CHCl₃) to afford (±)-camptothecin (26 mg, 47%) as a yellow solid: mp 275-277°C (mp 275-277°C reported in Volman, R.; Danishefsky, S.; Eggler, J.; Solomon, D.M., 25 J. Am. Chem. Soc. 1971, 93, 4074.).

EXAMPLE 14

Synthesis of (1R,4S,5R)-8-phenylmenthyl-(S)-2-(4-phenylbenzoyloxy)-2-(6'-chloro-2'-methoxy-3'-methoxymethyl-4'-pyridyl)butyrate

30 n-BuLi (1.86 M, 2.72 mL, 5.05 mmol) was added to a vigorously stirred solution of 6-chloro-4-iodo-3-methoxymethyl-2-methoxypyridine (1.51 g, 4.81 mmol) in 30 mL of THF at -78°C under Ar, and the mixture was 35 stirred for 1 min. A solution of (-)-8-phenylmenthyl 2-ketobutyrate (1.60 g, 5.29 mmol) in 3 mL of THF was added. The reaction mixture was stirred at -78°C for 1

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h after which a solution of 4-biphenylcarbonyl chloride (1.34 g, 7.22 mmol) in 3 mL of THF was added. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. Stirring was continued at room temperature for 36 h. The solvent was removed in vacuo and the residue was dissolved in 125 mL of CH_2Cl_2 . The mixture was washed with 40-mL portions of 10% aqueous NaHCO_3 , water and brine. The organic layer was dried over MgSO_4 and concentrated.

10 The residue was dissolved in 50 mL of ether and filtered through a short plug of silica gel. Concentration produced a light yellow solid which was dissolved in 30 mL of boiling petroleum ether (bp 37-55°C). The product precipitated upon standing at room

15 temperature overnight. After cooling to 0°C for several hours, the product was filtered and washed with a minimum of petroleum ether to produce 1.97 g (60% yield) of (1R,4S,5R)-8-phenylmenthyl-(S)-2-(4-phenylbenzoyloxy)-2-(6'-chloro-2'-methoxy-3'-

20 methoxymethyl-4'-pyridyl)butyrate as a white solid (mp 100-103°C). ^1H NMR: (300 MHz, CDCl_3) δ 8.22 (d, 2 H, $J = 7$ Hz), 7.05-7.80 (m, 13 H), 4.85 (m, 1 H), 4.50 (s, 2 H) 3.97 (s, 3 H), 3.16 (s, 3 H), 2.61 (m, 1 H) 0.55-2.35 (m, 21 H); ^1H NMR: (1R,4S,5R)-8-phenylmenthyl (R)-

25 2-(4-phenylbenzoyloxy)-2-(6'-chloro-2'-methoxy-3'-methoxymethyl-4'-pyridyl)butyrate (minor diastereomer): (300 MHz, CDCl_3), δ 8.22 (d, 2 H, $J = 7$ Hz) 7.05-7.80 (m, 13 H), 4.85 (m, 1 H), 4.62 (d, 1 H, $J = 9$ Hz), 4.35 (d, 1 H, $J = 9$ Hz), 3.90 (s, 3 H), 2.98 (s, 3 H), 2.62 (m, 1 H), 0.6-2.10 (m, 21 H).

EXAMPLE 15

Synthesis of (S)-2-hydroxy-2-(6'chloro-2'-methoxy-3'methoxymethyl-4'pyridyl)butyric acid by

5 Saponification of (1R,4S,5R)-8-phenylmenthyl (S)-2-(4-phenylbenzoyloxy)-2-(6'-chloro-2'-methoxy-3'-methoxymethyl-4'-pyridyl)butyrate

A solution of (1R,4S,5R)-8-phenylmenthyl-(S)-2-(4-phenylbenzoyloxy)-2-(6'-chloro-2'-methoxy-3'-methoxymethyl-4'-pyridyl)butyrate (201 mg, 0.294 mmol)

10 in 6 mL of a 1:1 ethanol/2N NaOH was heated at 85-90°C for 12 h. Most of the ethanol was removed under reduced pressure and the residue was diluted with water (3 mL) and extracted with ether (3 x 4-mL). It is

15 noteworthy that the chiral auxiliary ((-)8-phenylmenthol) was recovered in quantitative yield after evaporation of the ether extracts. The aqueous layer was acidified to a pH of 1 with 20% HCl and extracted with CH₂Cl₂ (3 x 5-mL). The combined organic

20 layers were washed with water (2 x 5-mL) and brine (5 mL) and were dried over anhydrous Na₂SO₄. Concentration produced 142 mg of crude product which upon ¹H NMR analysis was determined to be a 1:1 mixture of (S)-2-hydroxy-2-(6'chloro-2'-methoxy-3'methoxymethyl-

25 4'pyridyl)butyric acid and 4-biphenylcarboxylic acid. To this crude product was added 20 mL of hexanes, and, after bringing the solution to a boil, ethyl acetate was added dropwise until a clear homogeneous solution resulted. After standing at 25° overnight, the mixture

30 was filtered, the solids were discarded, and the filtrate was concentrated to afford a colorless semi-solid. This process was repeated using 5 mL of hexanes and 2-3 drops of ethyl acetate to remove additional 4-biphenylcarboxylic acid. After concentration of the

35 filtrate, 45 mg of (S)-2-hydroxy-2-(6'chloro-2'-methoxy-3'methoxymethyl-4-pyridyl)butyric acid (76% yield) was obtained as a colorless viscous oil. ¹H NMR

-35-

300 MHz (CDCl_3) δ 7.13 (s, 1 H), 4.81 (d, 1 H, $J = 13$ Hz), 4.55 (d, 1 H, $J = 13$ Hz), 3.96 (s, 3 H), 3.39 (s, 3 H), 2.19 (m, 2 H), 1.01 (t, 3 H, $J = 7$ Hz). This material was usable in subsequent synthetic steps 5 requiring an optically pure compound without further purification.

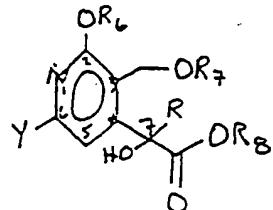
The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the 10 following claims, with equivalents of the claims to be included therein.

-36-

THAT WHICH IS CLAIMED IS:

1. A process for making a compound of the formula

5



(XIV)

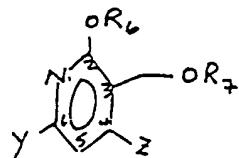
10

wherein R_6 is lower alkyl, R_7 is lower alkyl, R is lower alkyl, Y is H, F or Cl, and R_8 comprises a chiral moiety, comprising the steps of:

15

reacting a compound of the formula

20



(X)

wherein Z is Br or I, with a base of the formula

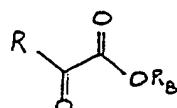
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 A^+B^-

wherein A^+ is an inorganic cation and B^- is an organic anion, to form an intermediate, then

stereospecifically adding to the intermediate
30 an α -keto-ester of the formula

35



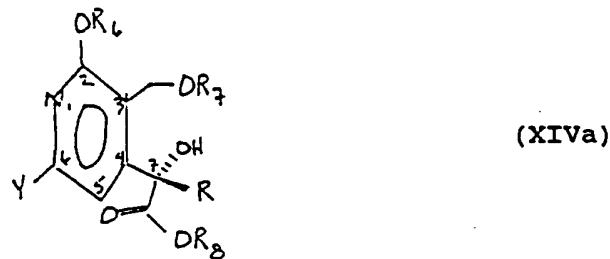
(XIII)

-37-

the R₈ moiety having a configuration that forces R and the -OH group of compound XIV to take a first stereochemical orientation about the chiral carbon at position 7 by sterically hindering the formation of an opposite second stereochemical orientation about the chiral carbon at position 7.

2. A process according to claim 1, wherein R₈ is optically pure, and wherein R and the -OH group of the compound of Formula XIV have the stereochemical orientation of formula XIVA:

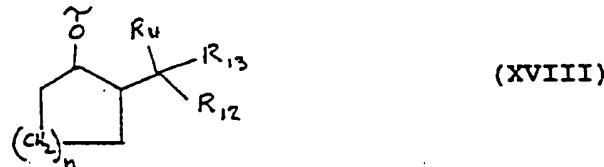
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20

3. A process according to claim 1, wherein R₈ comprises a moiety of Formula XVIII

25



30

wherein n is 1, 2, or 3, R₁₁ is a C₁-C₄ alkyl group and R₁₂ is the same as R₁₁, or R₁₁ and R₁₂ together form cyclopentane or cyclohexane, and R₁₃ is:

- (a) phenyl substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl, or
- (b) selected from the group consisting of naphthyl, anthryl, and phenanthryl optionally

-38-

substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl.

4. A process according to claim 1, wherein
5 R₁₁ and R₁₂ are both methyl or ethyl, and R₁₃ is phenyl
optionally substituted from 1 to 3 times at the 3, 4,
or 5 position with isopropyl or t-butyl.

5. A process according to claim 1, wherein
10 said process is carried out in an aprotic solvent
selected from the group consisting of tetrahydrofuran,
diethyl ether, dimethoxyethane, and toluene.

6. A process according to claim 1, wherein
15 said process is carried out in situ.

7. A process according to claim 1, wherein
said process is carried out in an inert atmosphere.

20 8. A process according to claim 1, wherein
R₆ is methyl.

9. A process according to claim 1, wherein
R₇ is methyl.

25 10. A process according to claim 1, wherein
R is ethyl.

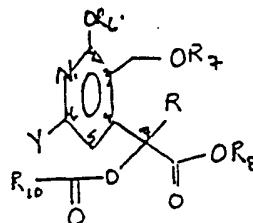
11. A process according to claim 1, wherein
30 B is n-butyl.

12. A process according to claim 1, wherein
the process is carried out at a temperature below 0°C.

35 13. A process for making a compound of the
formula

-39-

5

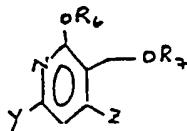


(XVII)

10 wherein R_6 is lower alkyl, R_7 is lower alkyl, R is lower alkyl, γ is H, F or Cl, R_8 comprises a chiral moiety, and R_{10} is C_6-C_{10} alkyl, aryl or alkyl aryl, comprising the steps of:

reacting a compound of the formula

15



(X)

20

wherein Z is Br or I, with a base of the formula

25

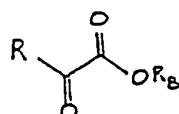


wherein A^+ is an inorganic cation, and B^- is an organic anion, to form a first intermediate, then stereospecifically adding to the first

30 intermediate an α -keto-ester of the formula

(XIII)

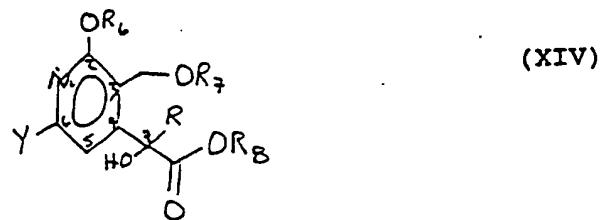
35



-40-

to form a second intermediate of the Formula XIV,

5



10 the R₈ moiety having a configuration that forces R and
the -OH group of compound XIV to take a first
stereochemical orientation about the chiral carbon at
position 7 by sterically hindering the formation of an
opposite second stereochemical orientation about the
15 chiral carbon at position 7, then
acylating the second intermediate with an
acyl halide of Formula XVI

20

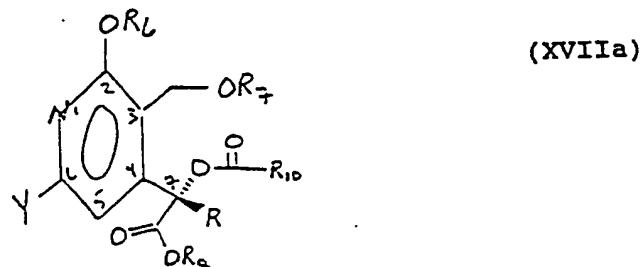


wherein X is Cl, I, or Br.

14. A process according to claim 13, wherein
25 R₈ is optically pure, and wherein R and R₁₀ have the
stereochemical orientation of formula XVIIa

30

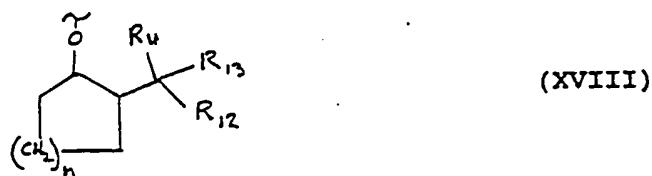
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-41-

15. A process according to claim 13, wherein
 R_8 comprises a moiety of Formula XVIII

5



10. wherein n is 1, 2, or 3, R_{11} is a C_1 - C_4 alkyl group and R_{12} is the same as R_{11} , or R_{11} and R_{12} together form cyclopentane or cyclohexane, and R_{13} is:

(a) phenyl substituted 1 to 5 times with C_3 - C_7 secondary alkyl or C_4 - C_7 tertiary alkyl, or

15. (b) selected from the group consisting of naphthyl, anthryl, and phenanthryl optionally substituted 1 to 5 times with C_3 - C_7 secondary alkyl or C_4 - C_7 tertiary alkyl.

20. 16. A process according to claim 13, wherein R_{11} and R_{12} are both methyl or ethyl, and R_{13} is phenyl optionally substituted from 1 to 3 times at the 3, 4, or 5 position with isopropyl or t-butyl.

25. 17. A process according to claim 13, wherein said process is carried out in an aprotic solvent selected from the group consisting of tetrahydrofuran, diethyl ether, dimethoxyethane, and toluene.

30. 18. A process according to claim 13, wherein said process is carried out in situ.

19. A process according to claim 13, wherein said process is carried out in an inert atmosphere.

35

20. A process according to claim 13, wherein R_6 is methyl.

-42-

21. A process according to claim 13, wherein
R₇ is methyl.

22. A process according to claim 13, wherein
5 R is ethyl.

23. A process according to claim 13, wherein
B is n-butyl.

10 24. A process according to claim 13, wherein
R₁₀ is selected from the group consisting of biphenyl,
anthryl, naphthyl, phenanthryl, and phenyl optionally
substituted from 1 to 5 times with C₁-C₃ alkyl groups.

15 25. A process according to claim 13 which
further comprises the step of recrystallizing the
compound of Formula XVII after the acylating step.

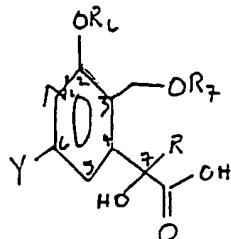
-43-

26. A process for making a compound of the formula

5

(XV)

10



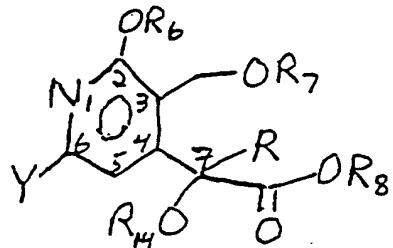
wherein R_6 is lower alkyl, R_7 is lower alkyl, R is lower alkyl, and Y is H, F or Cl, comprising the steps of:

15

saponifying a compound of the formula

20

(XIX)

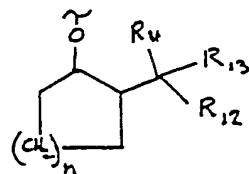


wherein R_8 comprises a moiety of Formula XVIII

25

30

(XVIII)



wherein n is 1, 2, or 3, R_{11} is a C_1-C_4 alkyl group and R_{12} is the same as R_{11} , or R_{11} and R_{12} together form cyclopentane or cyclohexane, and R_{13} is:

35

(a) phenyl substituted 1 to 5 times with C_3-C_7 secondary alkyl or C_4-C_7 tertiary alkyl, or

-44-

(b) selected from the group consisting of naphthyl, anthryl, and phenanthryl optionally substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl, and

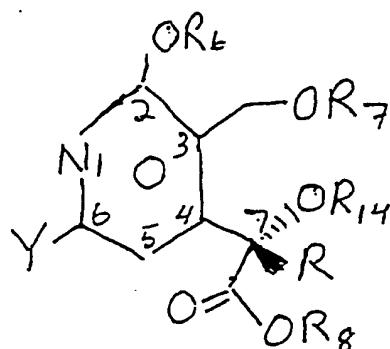
5 R₁₄ is hydrogen, C₆-C₁₀ alkyl carbonyl, aryl carbonyl or alkyl aryl carbonyl,
with a base to form a reaction intermediate;
then
protonating the reaction intermediate with
10 aqueous acid.

27. A process according to claim 26, wherein the compound of Formula XIX has the stereochemical orientation of Formula XIXa

15

20

(XIXa)



25

28. A process according to claim 27, wherein the compound of Formula XIX is diastereomerically pure.

29. A process according to claim 26, wherein the process is carried out in situ.

30

30. A process according to claim 26, wherein the saponification step comprises saponification with a mixture of ethanol and a metal hydroxide.

35

31. A process according to claim 26, wherein R₆ is methyl.

-45-

32. A process according to claim 26, wherein
R₇ is methyl.

33. A process according to claim 26, wherein
5 R is ethyl.

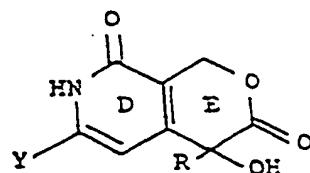
34. A process according to claim 26, wherein
R₁₁ and R₁₂ are both methyl or ethyl, and R₁₃ is phenyl
optionally substituted from 1 to 3 times at the 3, 4,
10 or 5 position with isopropyl or t-butyl.

35. A process according to claim 26, wherein
R₁₄ is selected from the group consisting of
biphenylcarbonyl, naphthylcarbonyl, anthrylcarbonyl,
15 phenanthrylcarbonyl, and phenylcarbonyl optionally
substituted 1 to 5 times with C₁-C₄ alkyl groups.

36. A process according to claim 26 wherein
the process further comprises recovering the chiral
20 auxiliary R₈ after the saponifying step.

37. A process for making a compound of the
formula

25



(III)

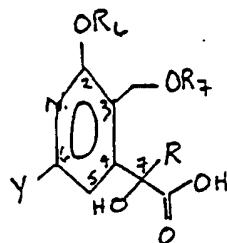
30

wherein R is lower alkyl, and Y is H, F or Cl,
comprising the steps of:

cyclizing a compound of the formula

-46-

5



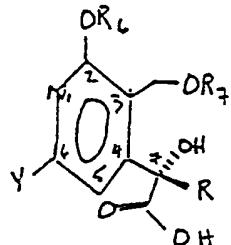
(XV)

10 wherein R_6 is lower alkyl, and R_7 is lower alkyl, with a trialkyl silane cyclizing compound in the presence of an aryl or alkyl amine to form an intermediate, then hydrolyzing the intermediate in aqueous acid.

15 38. A process according to claim 37, wherein the compound of Formula XV has the stereochemical orientation of Formula XVa

20

25



(XVa)

30

39. A process according to claim 37, wherein R is methyl.

30

40. A process according to claim 37, wherein said process is carried out in situ.

35

41. A process according to claim 37, wherein said cyclizing compound is iodotrimethyl silane.

-47-

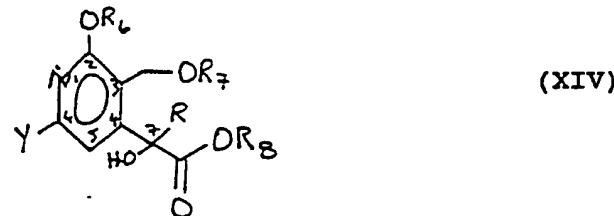
42. A process according to claim 37, wherein
said tertiary amine is triethylenediamine.

43. A process according to claim 37, wherein
5 said process is carried out in an aprotic solvent.

44. A process according to claim 38, wherein
the compound of Formula XVa is optically pure.

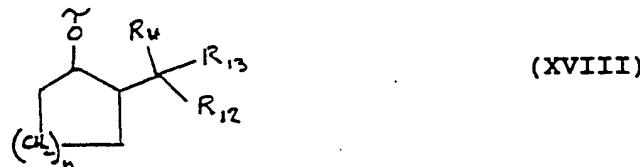
10 45. A compound of the formula

15



wherein R₆ is lower alkyl, R₇ is lower alkyl,
20 R is lower alkyl, R₈ is a moiety of Formula XVIII

25



wherein n is 1, 2, or 3, R₁₁ is C₁-C₄ alkyl and R₁₂ is the
30 same as R₁₁, or R₁₁ and R₁₂ together form cyclopentane or
cyclohexane, and R₁₃ is:

(a) phenyl substituted 1 to 5 times with C₃-C₇
secondary alkyl or C₄-C₇ tertiary alkyl, or

(b) selected from the group consisting of
35 naphthyl, anthryl, and phenanthryl optionally
substituted 1 to 5 times with C₃-C₇ secondary alkyl or
C₄-C₇ tertiary alkyl groups,

-48-

and Y is H, F or Cl.

46. A compound according to claim 45,
wherein R₆ is methyl or ethyl.

5

47. A compound according to claim 45,
wherein R₇ is methyl or ethyl.

48. A compound according to claim 45,
10 wherein R is ethyl.

49. A compound according to claim 45,
wherein R₁₁ and R₁₂ are both methyl or ethyl, and R₁₃ is
phenyl optionally substituted from 1 to 3 times at the
15 3, 4, or 5 position with isopropyl or t-butyl.

50. A compound according to claim 45,
wherein said compound has the stereochemical
orientation of Formula XIVa.

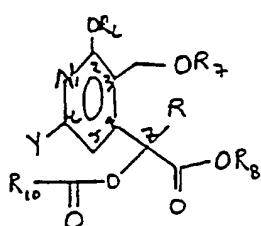
20

51. A compound according to claim 50,
wherein said compound is diastereomerically pure.

25

52. A compound of the formula

30



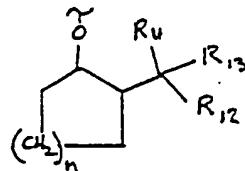
(XVII)

wherein R₆ is lower alkyl, R₇ is lower alkyl,
35 R₁₀ is aryl or alkyl aryl, R₈ is a moiety of Formula
XVIII

-49-

(XVIII)

5



wherein n is 1, 2, or 3, R₁₁ is a C₁-C₄ alkyl group and
 10 R₁₂ is the same as R₁₁, or R₁₁ and R₁₂ together form cyclopentane or cyclohexane, and R₁₃ is:
 (a) phenyl substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl, or
 (b) selected from the group consisting of
 15 naphthyl, anthryl, and phenanthryl optionally substituted 1 to 5 times with C₃-C₇ secondary alkyl or C₄-C₇ tertiary alkyl groups,
 R is lower alkyl,
 and Y is H, F or Cl.

20

53. A compound according to claim 52,
 wherein R₆ is methyl or ethyl.

54. A compound according to claim 52,
 25 wherein R₇ is methyl or ethyl.

55. A compound according to claim 52,
 wherein R₁₁ and R₁₂ are both methyl or ethyl, and R₁₃ is phenyl optionally substituted from 1 to 3 times at the
 30 3, 4, or 5 position with isopropyl or t-butyl.

56. A compound according to claim 52,
 wherein R₁₀ is selected from the group consisting of biphenyl, naphthyl, phenanthryl, and anthryl, and is
 35 optionally substituted from 1 to 5 times with C₁-C₄ alkyl groups.

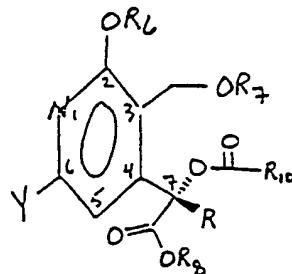
-50-

57. A compound according to claim 52,
wherein R is ethyl.

58. A compound according to claim 52,
wherein said compound has the stereochemical
orientation of Formula XVIIa

10

(XVIIa)



15

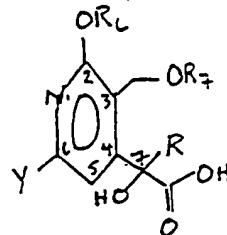
59. A compound according to claim 58,
wherein said compound is diastereomerically pure.

20

60. A compound of the formula

25

(XV)



30

wherein R₆ is lower alkyl, R₇ is lower alkyl,
R is lower alkyl, and Y is H, F or Cl.

61. A compound according to claim 60,
wherein R₆ is methyl or ethyl.

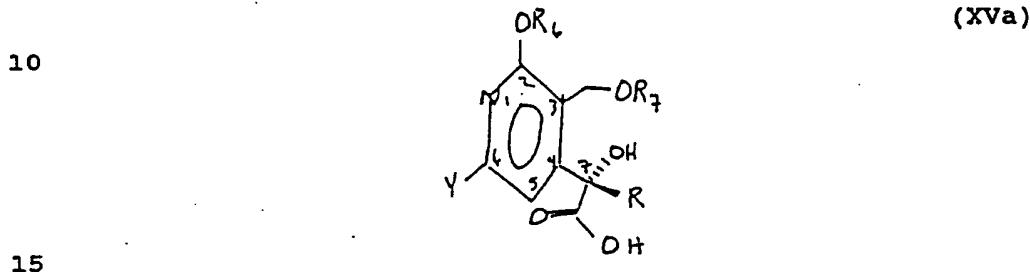
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62. A compound according to claim 60,
wherein R₇ is methyl or ethyl.

-51-

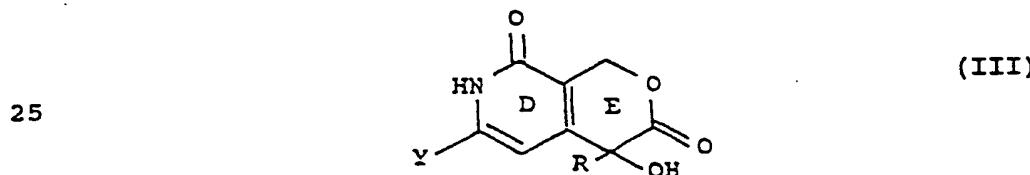
63. A compound according to claim 60,
wherein R is methyl.

5 64. A compound according to claim 60,
wherein said compound has the stereochemical
orientation of Formula (XVa)



65. A compound according to claim 64,
wherein said compound is optically pure.

20 66. A optically pure compound of the formula



30 wherein R is lower alkyl, and Y is H, F or
Cl.

67. A compound according to claim 66,
wherein R is methyl.

35 68. A compound according to claim 66,
wherein Y is Cl.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/03839

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 491/052, 213/64

US CL :546/116, 301, 302

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/116, 301, 302

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN - ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	US, A, 5,162,532 (Comins et al), 10 November 1992	1-68

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* "A" document defining the general state of the art which is not considered to be of particular relevance		
* "E" earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* "O" document referring to an oral disclosure, use, exhibition or other means	"Z"	document member of the same patent family
* "P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

07 JULY 1993

Date of mailing of the international search report

06 AUG 1993

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